

John J. Smith, MD, JD
A. Gregory Sorensen, MD
James H. Thrall, MD

Index terms:

Opinions
Radiology and radiologists, research
Radiology and radiologists,
socioeconomic issues

Published online before print

10.1148/radiol.2273020518
Radiology 2003; 227:633–638

Abbreviation:

FDA = Food and Drug
Administration

¹ From the Department of Radiology and MGH Center for Biomarkers in Imaging, Massachusetts General Hospital, 15 Parkman St, WACC 515, Boston, MA 02114. Received May 6, 2002; revision requested July 10; revision received August 13; accepted October 1. **Address correspondence to J.J.S.** (e-mail: smith.john@mgh.harvard.edu).

A.G.S. has consulted for and/or spoken on behalf of Berlex Laboratories/Schering.

© RSNA, 2003

Biomarkers in Imaging: Realizing Radiology's Future¹

Modern pharmaceuticals and medical devices have provided substantial benefits to patients throughout the world. These benefits come at a high and increasing cost, with development of the typical pharmaceutical requiring 12 years and hundreds of millions of dollars before gaining U.S. Food and Drug Administration marketing approval. Appropriate use of imaging biomarkers—defined as anatomic, physiologic, biochemical, or molecular parameters detectable with imaging methods used to establish the presence or severity of disease—offer the prospect of smaller, less expensive, and more efficient preclinical studies and clinical trials. Scientists, government regulators, and industry have all recognized the potential of biomarkers in imaging. Although real, this promise can only be realized with the rigorous application of science to their use. Success is most likely when (a) the presence of an imaging marker is closely linked with the presence of a target disease; (b) detection and/or measurement of the biomarker is accurate, reproducible, and feasible over time; and (c) measured changes are closely linked to success or failure of the therapeutic effect of the product being evaluated. By applying this paradigm to the array of imaging modalities, the radiology community is poised to become a major force in preclinical and clinical evaluations of new medical treatments.

© RSNA, 2003

Breakthrough advances in pharmaceutical therapy and medical devices have greatly contributed to the improved health and quality of life of people in the United States and throughout the world. Though these benefits are considerable, they come at a high price, with the typical new drug taking up to 12 years to develop and costing hundreds of millions of dollars to gain U.S. Food and Drug Administration (FDA) marketing approval (1). However, the creative use of imaging methods offers the prospect of improved early medical product development and preclinical testing, as well as the design of faster, smaller, and less expensive clinical trials, making the development of drugs and devices more efficient. In this article, we will review the practices and possibilities for the use of imaging biomarkers in drug and device development.

The key to understanding the emerging role of radiology in drug and medical device development is embedded in the concept of biomarkers. The generic term *biomarkers* applies to all detection methods used in the life sciences and may be defined as any detectable biologic parameter, whether biochemical, genetic, histologic, anatomic, physical, functional, or metabolic. By logical extension, we define imaging biomarkers as any anatomic, physiologic, biochemical, or molecular parameter detectable with one or more imaging methods used to help establish the presence and/or severity of disease. In this construct, what radiologists have traditionally referred to as “roentgen signs” are part of the broader concept of imaging biomarkers.

Biomarkers, including imaging biomarkers, have been recognized by clinical scientists, industry researchers, and regulatory bodies such as the FDA as suitable parameters around which to design clinical trials. The goal of the use of biomarkers is to speed the development of safe and effective medical therapies and procedures. In 1999, the National Institutes of Health and the FDA jointly sponsored a symposium entitled “Biomarkers and Surrogate Endpoints: Advancing Clinical Research and Applications.” Objectives of the conference included, among others, the following: to “encourage innovative collaboration among public and private partners in the clinical trials enterprise in evaluating biomarkers that may be used as surrogate endpoints” and to “broaden awareness in the scientific and medical community of substituting biomarkers for clinical endpoints in evaluating the safety and efficacy of novel therapies” (2).

The purpose of this commentary is to explore the limitations of traditional clinical trial end points as a motivation for the use of biomarkers and to review the statutory basis for the use of nontraditional surrogate end points such as imaging biomarkers in clinical trials. In addition, in this commentary we offer observations aimed at defining the necessary and sufficient conditions for validating the use of imaging biomarkers as surrogate end points and call attention to the important opportunities afforded by creative applications of biomarkers in imaging within the imaging community. By seizing these opportunities and building the science of biomarkers in imaging, our community can improve the efficiency of new medical product evaluation, ultimately improving care for those in need.

BACKGROUND: TRADITIONAL END POINTS AND THEIR ISSUES

The American public has long held high expectations for its medical therapies, as reflected by the elaborate regulatory controls established by the Food, Drug and Cosmetic Act (3). This legislation, administered by the FDA, requires that new drugs, devices, and biologics be safe and effective for their intended use(s).

The establishment of safety and effectiveness for genuinely new medical products often involves a lengthy and expensive period of preclinical and clinical trials (4). Preclinical trials, often conducted in animals, are typically used to demonstrate the safety of, as well as proof of concept for, a new therapy. If promising, the new product then proceeds to clinical trials in humans, a process that typically involves multiple stages commonly known as phases. These phases progress incrementally from small studies primarily designed to show the product's safety in humans, to much larger studies intended to establish effectiveness for a given disease or condition.

The reference standard for clinical trials is the prospective, randomized, well-controlled, double-blind study, originally developed to test the safety and effectiveness of new drugs (4). As the name implies, these studies are split into two groups, or "arms": In one arm, study participants receive the therapy; in the second arm, a control group traditionally receives no therapy other than a nontherapeutic placebo, although other types of controls may be used. During the trial, both the health care provider ad-

ministering the therapy and the patient are ideally unaware, or "blinded," as to whether the therapy or the placebo or control condition is being used. By using prospective subject recruitment, two study arms, and double blinding, a variety of potential experimental biases are avoided and the truest possible results can be obtained. While a number of other experimental constructs exist for clinical trials, the data from prospective, randomized, well-controlled, double-blind studies continue to be the most widely accepted by FDA and scientists alike.

Prospective, well-controlled, and double-blind and other clinical studies have historically used the traditional clinical end points of morbidity and mortality to establish whether the therapy under investigation is safe and effective, benchmarks also known as "true" end points. The classic end point of mortality determines whether the new therapy decreases the rate of death in comparison with that of a control group. A common example is 5-year survival in the setting of cancer therapies. Another traditional, yet broader, end point is morbidity, in which investigators examine whether patients undergoing the therapy are in some way more functional or enjoy a higher quality of life than do those who did not receive the therapy. An example is exercise tolerance following administration of a therapeutic agent in patients with asthma.

These traditional end points, while widely respected in the scientific and regulatory communities, are not without inherent limitations. Mortality, although straightforward to measure, often takes years of follow-up to establish, adding considerable cost and delay to the evaluation of safe and effective new treatments. Time frame notwithstanding, patients are also frequently lost to follow-up, experience intercurrent illness, or undergo additional therapy, which further complicate the use of this end point. The determination of morbidity, although potentially involving a shorter evaluation time frame, is often considerably more subjective. For example, use of pain as an end point in trials to examine the effectiveness of analgesic medications has traditionally involved patient estimation of pain levels, with essentially no ability to verify data objectively.

Apart from the difficulty in evaluating traditional end points themselves, there may be considerable technical issues in the application of a prospective, randomized, well-controlled, double-blind study

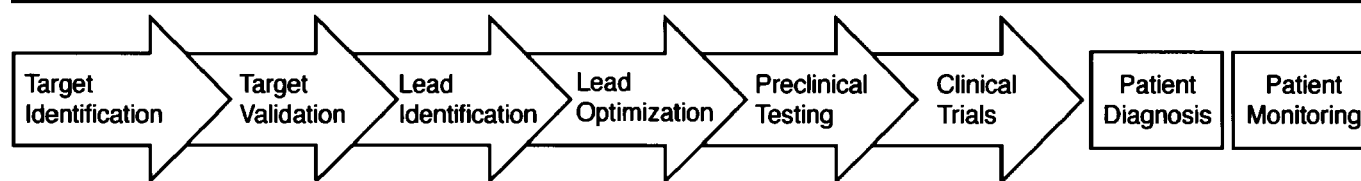
design to a given trial. Initially, prospective recruitment of suitable patients in sufficient numbers may prove difficult or impossible. This is particularly true when a disease has a low prevalence or affected patients are aggressively seeking other traditional or nontraditional treatments (not an uncommon occurrence in an environment where patients often perceive treatment of any kind to be beneficial). A frequently cited example of the latter was clinical testing of early AIDS medications, where it was difficult to find patients willing to give up use of a variety of unproven remedies in order to take part in clinical studies (5).

Ethical issues may also affect the use of traditional placebo-control groups. When there is an existing clinically accepted treatment for the condition being evaluated, it is unethical to withhold that treatment, which makes possible only a comparison to the existing treatment. There are also substantial issues when a sponsor is seeking an additional indication for an existing medical product that has already been extensively used "off label" to treat that indication and when such use may be considered the standard of care. This situation recently arose when sponsors sought to establish the safety and efficacy of pedicle screws for posterior spinal fixation. The products had already been extensively used in an off-label manner and were considered by many to be the medical standard of care, effectively eliminating the possibility of a traditional placebo-control group (6).

Even when a prospective, randomized, well-controlled, double-blind study is technically and ethically feasible, the high cost and long time frame typically involved in such studies have a substantial impact (1). High cost may discourage sponsors from focusing on all but "blockbuster" products that address the needs of large groups of affected patients so that the return on any investment may be maximized. Cost may also prevent smaller firms from undertaking clinical studies entirely. Perhaps most important, the substantial time commitment required to conduct prospective, well-controlled, double-blind studies may unduly delay the widespread clinical introduction of safe and effective treatments, keeping the treatments from patients who could directly benefit from the therapy.

BIOMARKERS IN IMAGING: A VEHICLE FOR CHANGE

Every day, radiologists assess findings in imaging studies that gauge the effective-



Typical industrial product-development pathway outlines steps necessary to initially identify a promising site of therapeutic action and potential therapy that affects that site and then validate that therapy for clinical use. In this diagram, targets are typically molecular steps or events in the physiology or pathophysiology that could be targeted with new therapies, such as a receptor or a signal transduction pathway. "Leads" are novel compounds or devices that might act on such targets.

ness of medical treatments. These imaging biomarkers range from simple measurement of tumor mass to cutting-edge magnetic resonance (MR) imaging sequences developed to enable evaluation of the presence of cerebral ischemia. The benefit of these techniques is obvious to the patient being evaluated and the health care providers coordinating that patient's care. However, a broader and potentially more important use of these techniques is the systematic evaluation of the therapies themselves, where the imaging biomarkers become surrogate end points for clinical trials.

Key to the enormous potential of imaging biomarkers is the reality that many medical therapies alter the anatomic, physiologic, biochemical, or molecular parameters readily visualized with imaging techniques. Particularly with established modalities such as conventional radiography, computed tomography (CT), or MR imaging, a large pool of existing imaging technologies may be brought to bear in a cost-effective manner to help assess the presence and severity of many diseases. Even imaging modalities that are not yet FDA approved and not generally applicable in patients may be used effectively in preclinical decision making, as is the case with a number of molecular imaging methods.

The U.S. Congress and FDA have recognized the potential of nontraditional "surrogate" end points in both preclinical and clinical trials, a concept that easily encompasses imaging biomarkers and was recently defined by a senior FDA official as follows: "A laboratory measurement or physical sign used as a substitute for a clinically meaningful end point that measures directly how a patient feels, functions, or survives. Changes induced by a therapy on a surrogate end point that are expected to reflect changes on a clinically meaningful end point" (7).

The most recent and important applicable law is the Food and Drug Administration Modernization Act of 1997 (8), which was enacted to address perceived

shortcomings in the existing medical product regulatory process. A key provision is section 112 of the act, which addresses speeding the approval of drugs intended to treat any serious or life-threatening condition. Covered conditions are broadly defined to encompass diseases that affect day-to-day functioning or those for which a likelihood of progression from a less serious state exists if the condition is left untreated. This definition is thought to include virtually any medical condition of consequence.

Under section 112, marketing approval for a drug may be secured when the FDA makes the determination that the product has an effect on a surrogate end point that is reasonably likely to predict clinical benefit. This was the case when T2-weighted MR imaging demonstration of lesion burden was used for in the approval process for interferon- β -1b (Betaseron; Berlex Laboratories, Montville, NJ) for treatment of multiple sclerosis (9). Additional provisions allow for surveillance after marketing approval to help confirm the validity of the surrogate end point. Finally, the FDA is required to establish a program to encourage the development of surrogate end points that are reasonably likely to help predict clinical benefit for serious or life-threatening conditions for which there exist substantial unmet medical needs. Together, these provisions form a strong regulatory foundation for the appropriate use of imaging biomarkers for drug-related trials.

The Food and Drug Administration Modernization Act does not specifically address surrogate end points in the evaluation of medical devices. However, section 205 of the act requires that the agency use the "least burdensome means necessary" in granting marketing approval for medical devices (10). Though considerably more general than the drug provisions, the least-burdensome-means concept is widely believed to include the appropriate use of surrogate end points in preclinical and clinical trials, because evaluation of such end points may be

considerably less burdensome than evaluation of traditional end points. As with the drug provisions of section 112, section 205 provides a strong legal basis for the application of imaging biomarkers in clinical and preclinical trials.

The pharmaceutical and medical devices industries have also acknowledged the considerable promise of biomarkers in general and, by analogy, biomarkers in imaging, largely focusing on the potential of biomarkers to increase efficiency in preclinical and clinical evaluations of new therapies. The trade literature is replete with discussions of biomarkers, as can be seen in a recent trade journal article (11) in which the appropriate application of biomarkers in medical product development was explored in depth, complete with a thoughtful analysis of their usefulness and inevitable limitations. This article also outlined the steps those in industry view as necessary to bring a new medical product to market (a paradigm outlined in the Figure), linking those steps to where biomarkers may be used. Table 1 indicates areas in which imaging biomarkers may play an important role within this paradigm.

Imaging biomarkers, potentially useful as surrogate end points, exist everywhere in radiology. One of the most commonly used is the measurement of tumor size in primary neoplasms or metastatic disease in patients undergoing chemotherapy or radiation therapy. MR signal alterations in white matter are frequently used to assess activity in patients being treated for multiple sclerosis. Even such straightforward findings as vertebral body height have been effectively used to evaluate patient response to pharmacologic treatments for osteoporosis. Table 1 notes biomarker imaging modalities applicable to the various stages of industry's product-development paradigm.

Beyond traditional clinical applications, many imaging modalities may be used with animals in the preclinical setting. These include FDA-approved modalities applicable in patients, as well as

non-FDA-approved cutting-edge technologies such as molecular imaging with nuclear, MR, or optical techniques (12). Thoughtful use of biomarkers in these situations may allow early safety and proof-of-concept determinations and perhaps further reduce the number of animals necessary to successfully complete preclinical studies to the satisfaction of FDA. Perhaps more important, biomarker use in the preclinical setting may allow researchers to identify promising new therapies more quickly, as well as convincingly demonstrate that other products hold no such promise, greatly improving the efficient evolution of the vast number of drugs and devices in initial stages of evaluation.

The use of imaging biomarkers in early stages of development is particularly useful given three aspects of the modern paradigm for drug development. First, in large pharmaceutical and device companies, a large number of candidate therapies are available, and the key question facing developers is how to choose among many competing compounds or devices. Given finite resources, the choice of investment in one drug or device necessarily means no investment in another, and the central challenge becomes management of a portfolio of competing candidates. The early-stage information that imaging biomarkers can provide is particularly valuable to those who make these choices. Second, imaging provides (perhaps uniquely) the ability to validate in humans the results identified in successful animal model experiments. This validation allows early feedback about numerous key questions ranging from dose effectiveness to validation of the presumed biologic mechanism of action. Finally, in modern medicine, advancement against disease is typically incremental, and imaging can potentially reveal smaller and more subtle changes indicative of incremental changes that might be missed with traditional evaluation approaches.

Beyond the application to these three fundamental aspects of modern development, imaging biomarkers have other advantages. Initially, they may be effectively used to address many of the inherent limitations associated with traditional end points in preclinical and clinical trials. For example, imaging findings are often apparent long before long-lead-time parameters such as mortality can be accurately assessed, allowing a compressed evaluation time frame. Similarly, findings obtained with a variety of imaging modalities may be far less sub-

TABLE 1
Roles of Imaging Biomarkers

Product Development Stage	Applicability of Imaging Biomarkers	Imaging Modality
Target identification	Yes	Nuclear medicine, PET, other molecular imaging approaches
Target validation	Yes	Nuclear medicine, PET, other molecular imaging approaches
Lead identification	No	None
Lead optimization	Yes	Nuclear medicine, PET, other molecular imaging approaches
Preclinical testing	Yes	Nuclear medicine, PET, other molecular imaging, CT, MR
Clinical trials	Yes	CT, MR, US, nuclear medicine, PET, conventional radiography
Diagnosis	Yes	CT, MR, US, nuclear medicine, PET, conventional radiography
Patient monitoring	Yes	CT, MR, US, nuclear medicine, PET, conventional radiography

Note.—PET = positron emission tomography, US = ultrasonography.

jective than those acquired with morbidity evaluations as currently conducted. An illustration of this potential can be seen in the functional MR imaging evaluation of pain, a technique that may hold the promise of a more objective determination than the patient-determination method presently in use (13).

Imaging biomarkers also have the potential to address many of the technical and ethical issues concerning prospective, randomized, double-blind, placebo-controlled studies. Initially, creative use of biomarkers may allow each patient to serve as his or her own control in certain settings, greatly reducing the number of patients required to achieve statistical significance and saving both time and resources. For example, algorithms are being developed for accurate and dependable prediction of untreated cerebral infarct size in ischemic stroke, using perfusion and diffusion information obtained with MR imaging in the hyperacute phase (14). Patients may then undergo treatment, with the ultimate area of ischemia evaluated at a later date and compared with the predicted outcome if untreated, eliminating the profound ethical issues associated with foregoing any treatment for this potentially debilitating condition.

Issues associated with double blinding, particularly with regard to medical devices, may be effectively addressed by using appropriate imaging biomarkers. For example, it may be virtually impossible to blind a radiologist using a new device in a clinical trial as to whether he or she is using the product actually being tested. However, it may be relatively easy to blind a radiologist who subsequently

evaluates a trial-associated imaging biomarker as to which product was used in which patient. Even with new pharmaceuticals, the use of imaging biomarkers evaluated by individuals with no subject or patient contact can be extremely useful in limiting bias related to the lack of effective investigator blinding.

Even in the context of these limited examples, outlined in Table 2, it is easy to see how everyday radiologic findings may be effectively used as imaging biomarkers. Perhaps just as important, many of these parameters may be evaluated by using imaging modalities that are widely available nationwide, providing a tremendous infrastructure on which to build biomarkers-related trials. With both versatility and practicality, imaging biomarkers have enormous potential to aid in a wide variety of preclinical and clinical trials.

DEVELOPING THE BIOMARKERS CONCEPT

Imaging biomarkers have enormous potential to improve the speed and efficiency with which medical therapies are evaluated. As is the case with any evaluation tool, however, there are limitations. While promising, imaging biomarkers are not and should never be considered a solution to every preclinical or clinical question. Application of biomarkers in a manner that is less than fully considered runs the distinct risk of generating results that are inaccurate or incomplete. Importantly, it does not require many such failures to generate a lack of confidence in the biomarkers con-

TABLE 2
Biomarkers in Imaging versus True or Traditional End Points

Parameter	True or Traditional Endpoints	Imaging Biomarkers
Time frame to results	May be long, particularly when mortality used	Potential for substantially shorter results time frame
Objectivity	May be low when morbidity or similarly subjective end point is used	Potential for increased objectivity where end points other than mortality are used
Cost	High, particularly when mortality or other long-term end point is used	Relatively low compared with long-term true or traditional end points
Ability to achieve blinding	May be difficult, particularly with medical devices	Relatively easy in the setting of blinded readers
Ability to detect subtle change	Often low	Routine ability to detect small changes on images
Ability of patient to serve as own control	Possible, but may be difficult in practice	Possible in many instances
Access to required resources	Widespread but expensive, dedicated infrastructure required	Widespread, with cost of imaging infrastructure largely defrayed by routine clinical use

cept that could extend far beyond a few poorly designed applications.

Given this potential for negative impact, it is imperative that imaging biomarkers used in preclinical and clinical decision-making be appropriately validated for use as surrogate end points for the application at issue. Such validation may be established when the following three criteria are met: (a) The presence of the imaging biomarker is closely coupled or linked to the presence of the target disease or condition; (b) the detection and/or quantitative measurement of the imaging biomarker is accurate, reproducible, and feasible over time; and (c) the measured changes over time in the imaging biomarker are closely coupled or linked to the success or failure of the therapeutic effect and the true end point sought for the medical therapy being evaluated (15–17).

To understand this validation process, it is useful to review examples of its application to familiar imaging biomarkers. CT scans are often used to evaluate metastatic disease to the liver. Tumor volume is the imaging biomarker, with a reduction in volume the desired therapeutic effect and decreased patient mortality over a period of time the traditional or true end point. Use of CT in the detection of liver lesions is closely linked to metastatic disease, and CT measurement of tumor volume is accurate, reproducible, and feasible over time. Furthermore, reduction in tumor volume in response to therapy may be easily measured, and such reduction has been linked to prolonged survival (18). Since CT measurement of liver lesion volume meets the

validation criteria for an imaging biomarker, it may be confidently used in this role, as it has been in the past for drugs such as trastuzumab (Herceptin; Genentech, South San Francisco, Calif).

This paradigm may also be used to exclude the use of certain imaging findings as biomarkers. For example, bone densitometry can be used to provide accurate measurements of bone mineral density in osteoporosis and allow accurate and reliable identification of bone mineral density changes in response to therapy. However, such measurements do not help in assessment of trabecular architecture or overall bone strength, a crucial true end point in therapy to reduce the risk of insufficiency fracture. In this case, without a strong link to the true end point sought, bone densitometry does not meet the criteria for a valid biomarker in imaging, despite its routine use in the diagnosis of osteoporosis. Instead, conventional radiographs, which can depict a fracture, would be a superior imaging biomarker.

When validating an imaging biomarker, other crucial considerations include the side-effect profile or toxicity of the therapy being evaluated and whether the contemplated biomarker demonstrates these findings. Biomarkers that show therapeutic effects of a drug may not allow adequate assessment of untoward effects of that drug, leading to the possibility of a dangerously incomplete evaluation. For example, it is entirely possible that a chemotherapy trial designed around an imaging biomarker, such as CT measurement of tumor volume, could accurately demonstrate a meaningful therapeutic effect

while completely missing serious cardiotoxicity. Accordingly, such effects must be carefully considered when imaging biomarkers are used. Indeed, because so many new drugs fail clinical development because of safety issues, imaging biomarkers that can provide insight into toxicity may have value in their own right.

Ultimately, scientists and regulators are most likely to accept surrogate end points that have been well studied and characterized in large groups of patients, because such large studies are likely to minimize the possibility of unexpected and inaccurate results that might reflect limited experience with a given surrogate end point. In a well-known example in the cardiology community, antiarrhythmic agents were believed to provide an increased survival benefit to patients after myocardial infarction. This belief was based on the observation that such arrhythmias were a frequent cause of death and on the clinical demonstration that these agents did in fact reduce such arrhythmias. However, when the effect of these drugs on survival was directly measured in a well-controlled trial, the therapy was found to substantially increase mortality, much to the surprise of the investigators (19). This and similar experiences demonstrate how even logically appealing surrogate end points benefit from a validation process that incorporates extensive patient experience. Importantly, such patient experience may be feasible for many imaging biomarkers, given their widespread use in numerous clinical settings.

There are some instances where an imaging biomarker might still be useful despite minimal validation. For example, a novel molecular imaging approach might be so new that only limited experience is available in a given application, but even preliminary data might provide valuable insight. In this situation, the validation might be more appropriately described as technical or limited validation rather than clinical validation. The imaging test must still be trustworthy, but it may not have been widely used in clinical practice; therefore, the limits of its validity may be narrow.

Imaging biomarkers that meet the validation paradigm set forth above or other suitable validation paradigms have enormous potential to provide value in preclinical and clinical settings. However, to realize this potential there must be an organized and determined effort on the part of radiologists and the broader medical community. This necessarily includes research to determine what exist-

ing anatomic, physiologic, biochemical, or molecular imaging parameters may be useful as surrogate end points, as well as where they may be applied. It is particularly important that this information be made easily available to decision makers in government and industry to ensure that the expanded use of biomarkers is fully exploited. Finally, when use of an imaging biomarker is seriously considered, that particular biomarker must be fully validated for the setting in which it is to be applied, by using the paradigm described in this article or other similarly rigorous criteria.

The Department of Radiology at the Massachusetts General Hospital, Boston, has already taken the first steps in what is hoped to be a determined effort on the part of the radiology community to answer the challenge created by imaging biomarkers. In April 2001, the MGH Center for Biomarkers in Imaging was founded. The center is dedicated to furthering knowledge about biomarkers through several discrete efforts. Initially, the center is attempting to catalog biomarkers present at MGH; as resources permit, this effort will be extended beyond the center. This information is readily available to interested physicians, scientists, industry representatives, and regulators on the center's Website (www.biomarkers.org). In the future, an assessment of the degree of validation of each biomarker may be added. As specific interests are identified and resources allow, the center will undertake rigorous scientific research to fully validate those biomarkers that may be useful to decision makers in clinical practice, government, and industry.

Through these and related efforts, we hope that the radiology community in general and academic radiology in particular become active participants in the identification, development, and validation of imaging biomarkers, applying this science to the evaluation of new medical products. This would necessarily involve the publication of scholarly re-

search addressing the appropriate use of imaging biomarkers in the peer-reviewed medical literature. Industry is likely to be a key participant in these efforts by providing resources to evaluate imaging biomarkers of interest and as a funding source with the potential to broadly support and substantially expand medical imaging research.

Imaging biomarkers are only as strong as the scientific foundation on which they are built, and the MGH Center for Biomarkers in Imaging alone cannot possibly achieve the full promise of imaging biomarkers. The broader radiology community, including professional societies, institutions, and individual radiologists, must become engaged in the biomarkers concept, fostering both the underlying science and the practical application of these important tools. By working together, the radiology community can and will achieve the full benefits of imaging biomarkers, including improved early medical product development and preclinical testing, as well as more efficient clinical trials. In doing so, our community will ultimately provide a sounder scientific basis for all medical imaging and the care we provide our patients.

References

1. Tollman P, Guy P, Altshuler J, Flanagan A, Steiner M. A revolution in R&D: how genomics and genetics are transforming the biopharmaceutical industry. Boston Consulting Group, November 2001. Available at: www.bcg.com/publications/files/eng_genomicsgenetics_rep_11_01.pdf. Accessed April 24, 2002.
2. National Institutes of Health and Food and Drug Administration. Biomarkers and surrogate endpoints: advancing clinical research and applications—a multidisciplinary, international conference sponsored by NIH and FDA. Available at: www4.od.nih.gov/biomarkers/. Accessed February 13, 2003.
3. 1938 Federal Food, Drug, and Cosmetic Act. Pub L No. 75-717, 52 Stat 1040, 21 USC §301–§394.
4. Merrill RA. The architecture of government regulation of medical products. *Virginia Law Rev* 1996; 82:1753–1866.
5. Annas GJ. Faith (healing), hope and charity at FDA: the politics of AIDS drug trials. *Villanova Law Rev* 1989; 34:771–797.
6. Orthopedic devices: classification, reclassification, and codification of pedicle screw spinal systems. 60 Federal Register 51946–51957 (1995).
7. Temple RJ. A regulatory authority's opinion about surrogate endpoints. In: Nimmo WS, Tucker GT, eds. *Clinical measurement in drug evaluation*. New York, NY: Wiley, 1995.
8. Food and Drug Administration Modernization Act of 1997. Pub L No. 105-114, 111 Stat 2296, 21 USC §301–§394 (1997).
9. Food and Drug Administration. Licensing approval notice for Betaseron (July 23, 1993). Available at: www.fda.gov/bbs/topics/NEWS/NEW00424.html. Accessed July 21, 2002.
10. Smith JJ, Shyjan AM. Defining “least burdensome means” under the Food and Drug Administration Modernization Act of 1997. *Food Drug Law J* 2000; 55:435–447.
11. Kumar G. Marking the future. *Biocentury* 2002; 10:A1–A5.
12. Weissleder R. Scaling down imaging: molecular mapping of cancer in mice. *Nat Rev Cancer* 2002; 2:11–18.
13. Tracey I, Becerra L, Chang I, et al. Noxious hot and cold stimulation produce common patterns of brain activation in humans: a functional magnetic resonance imaging study. *Neurosci Lett* 2000; 288:159–162.
14. Wu O, Koroshetz WJ, Ostergaard L, et al. Predicting tissue outcome in acute human cerebral ischemia using combination diffusion- and perfusion-weighted MR imaging. *Stroke* 2001; 32:933–942.
15. Schatzkin A, Gail M. The promise and peril of surrogate endpoints in cancer research. *Nat Rev Cancer* 2002; 2:19–27.
16. Prentice RL. Surrogate markers in clinical trials: definitions and operations criteria. *Stat Med* 1989; 8:431–440.
17. Fleming TR, DeMets DL. Surrogate endpoints in clinical trials: are we being misled? *Ann Intern Med* 1996; 125:605–613.
18. Buyse M, Thirion P, Carlson RW, Burzykowski T, Molenberghs G, Piedbois P. Relation between tumor response to first time chemotherapy and survival in advanced colorectal cancer: a meta-analysis—Meta-Analysis Group Cancer. *Lancet* 2000; 356:373–378.
19. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991; 324:781–788.